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14. ABSTRACT
Despite administrative difficulties that delayed the initiation of the protocol parts involving human subjects, we have completed testing and training of 20 control subjects. There was a remarkable improvement in the objective measurements of the visual functions, including subjective improvement reported by the subjects. Based on the accumulate data, we prepared an updated set of pretest/posttest and training protocol in order to improve the training results, especially in the periphery. The results of the training suggest that we will be able to apply a modified protocol to TBI patients. Though it was not planned in the original proposal, we will run another subset of controls to validate the improved protocol in order to increase the efficacy of the training protocol. We will present the data in the 3rd International Workshop on Perceptual Learning in December 2012 and will prepare a manuscript for publication based on the data of all controls subjects. We have recruited 6 TBI patients so far and present the results of a representative TBI patient. There is already a pronounced improvement in his visual acuity, of more than 1 ETDRS line, towards the levels of the normal control group, in static contrast sensitivity and in lateral interactions, with the negative effect of lateral masking replaced by a slight positive effect of facilitation (i.e., detection threshold reduction). He also reports subjective improvement. We proceed with training of patients and intensive screening the medical files to identify more potential TBI patients.

15. SUBJECT TERMS
Traumatic Brain Injury; Perceptual Learning; Behavioral Treatment; Visual Dysfunction; Cortical Plasticity

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Introduction

Different traumatic brain injuries are associated with visual dysfunction (Chua, Ng, Yap & Bok, 2007). Tissue damage following stroke, car accident, etc. may result in visual scotomas or other severe visual deficits. Accumulating evidence suggests that the adult visual cortex retains significant potential for experience-dependent plasticity (Fahle, 2002). A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. Plasticity is based on neuronal excitations and is affected by pharmacological changes in the balance between neuronal excitation or inhibition (He, Hodos & Quinlan, 2006, Maya Vetencourt, Sale, Viegi, Baroncelli, De Pasquale, O'Leary, Castren & Maffei, 2008, Rozas, Frank, Heynen, Morales, Bear & Kirkwood, 2001).

A method developed in our laboratory is a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations. Neuronal interactions in the visual processing were robustly affected by changes in the balance between excitations and inhibitions. We applied our paradigm to treat abnormal neuronal interactions in amblyopic adults (Polat, 2008, Polat, Ma-Naim, Belkin & Sagi, 2004). We were the first to show plasticity in adults with a visual deficit that was considered untreatable, see below. Using a similar paradigm, we also achieved a significant improvement in individuals with presbyopia, see below (Polat, 2009, Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin & Levi, 2012). Thus, our treatment induces visual enhancement of blurred or low-contrast images, an effect that is highly applicative for patients with visual dysfunction associated with TBI. Moreover, our recent study with similar paradigm resulted in improved visual functions in young subjects with normal vision in only 10 training sessions (Sterkin, Yehezkel & Polat, 2012). We have a highly efficient and practical treatment technique to improve vision. Thus, we can apply this proved effective training techniques to evoke plasticity in the damaged visual cortex of patients with TBI. The training paradigm is intended to reduce the extent of the damaged visual fields (i.e., "restitution training").

Body

During the last quarter of the research period, we have continued to train and posttest control subjects. So far, 20 control subjects finished the training and we present here the results, although over 30 were initially recruited. There was a remarkable improvement in the objective measurements of the visual functions, including subjective improvement reported by the subjects. So far, we have recruited 6 TBI participants. We anticipated that the pre-treatment phase of the TBI patients will require personal adjustments for each patient. Indeed, due to different type of the injury of each patient, that involve cognitive and motor limitations, we were required to personalize the psychophysical testing to the abilities of each patient. For example, such adjustments were done in the presentation time of the stimuli, adding sounds to mark the presentation time and colored symbols to ease with the detection of the temporal interval. We are also exploring alternative methods, such as voice recognition and foot pedals instead of standard mouse key, for collecting the response from the patients. All these adjustments require continued programing modifications and retesting. Moreover, due to physical and transportation limitations, the amount of collected data in each session is limited compared to control data. As a result, the period of the pre-treatment sessions is much longer than initially anticipated. On the other hand, this period is also necessary and can be considered as instruction period that is needed for the patients to comprehend the training procedures.

Obviously, the adjustment of the pretesting is posing the requirement to re-test control subjects on the modified parameters that the TBI patients were tested in order to have normative data.

We are aiming to perform part of the training at the TBI's homes. This option is suggested by the Review Expert Panel and may reduce the burden from the patients to arrive few times a week to the lab. To do so, we are helping them in purchasing computers, instructions on internet connection and other technical issues that needed to be resolved for remote training. We will install the training program and receiving/sending the training sessions via the internet. From time to time we will ask them to visit the lab to validate the quality of the data. One patient preferred to be trained on his i-Phone. We installed the Ucani Inc. application and will train him using a training program tailored to his abilities. In general, establishing efficient training protocol for TBI patients is very challenging and requiring creative solutions tailored to each patient. We anticipate that this solution will accelerate the pace of training.

We are facing a technical issue of slow rate of patient recruitment. This is due to the fact that one of the in-charged Neurologists moved to another medical center. The new Neurologist is already participating in the study. For this reason, and due to the difficulty of recruiting patients from only one medical center, we are in the process of adding another Neurologist from another medical center to accelerate the pace of patient recruitment.

Task 1. To apply behavioral training to healthy control individuals using our paradigm that is adapted for peripheral vision. This experiment will provide us with exact indications on potential effectiveness of the treatment and the amount of expected improvement in the target populations (months 1-12):

1a. Modification of the software for periphery (months 1-2).

Was accomplished as reported earlier.

1b. Adapting the eye-tracking system for the new setup (months 3-4).

Was accomplished as reported earlier.

1c. Creating of Matlab interface for interpretation of the eye-tracking results (months 3-4).

Was accomplished as reported earlier.

1d. Healthy participants recruitment and screening (months 3-9).

We have completed recruiting all control subjects.

1e. Baseline testing of the healthy participants (3-9)

Was accomplished as reported earlier (see section 1f below).

1f. Training of the healthy participants (months 3-12).

Twenty control subjects finished the training and we present here their results. All measurements of the visual functions are shown before (pretest) and after (posttest) completing 20 training sessions (each session on a different day).

The visual acuity measure with an acuity chart and the stereo acuity improved after training, as well as the more sensitive measure of acuity – letter crowding – that was significantly improved both for the lower and the higher letter densities.

Moreover, contrast sensitivity for transient targets at different contrasts was significantly improved by the training for all contrasts in the periphery and for the lowest contrast in the fovea.

There were also clear effects of the lightening conditions and of the spatial frequency on contrast detection of static targets, with significant improvement for the lowest spatial frequency under "Day" conditions and for the two lower spatial frequencies for the "Night" conditions.

Finally, there were no changes in the gaze position induced by training in normal controls, indicating that the improvements in the visual functions induced by training <u>cannot be accounted for by gaze stabilization mechanism</u>, thus we can conclude that the changes occurred in the brain.

Based on the accumulate data, we prepared an updated set of pretest/posttest and training protocol in order to improve the training results, especially in the periphery. Though it was not planned in the original proposal, we will run another group of controls to validate the improved protocol in order to increase the efficacy of the training protocol. We will present the data in the 3rd International Workshop on Perceptual Learning in December 2012 and will prepare a manuscript for publication based on the data of all controls subjects.

The detailed summary of the results of the healthy control participants:

Eye movements:

Figure 1 shows results for a representative subject: the trajectories of eye movement in the vertical and the horizontal directions. The data presented in Figure 2 (N=18, 2 outliers above 2 STD) refers to all trials (both with True and False responses), in the range [-100,500 milliseconds] relative to stimulus onset. Figure 2 (left panel) shows the average of the per-trial standard deviation of mean position, i.e. the "quality" parameter for each trial that is the variability of the gaze position in the given time range. Figure 2 (right panel) shows the standard deviation of the above variability, i.e. the gaze stability across the session. As can be easily seen, there were no changes in the gaze position induced by training in normal controls, indicating that the improvements in the visual functions induced by training cannot be accounted for by gaze stabilization mechanism.

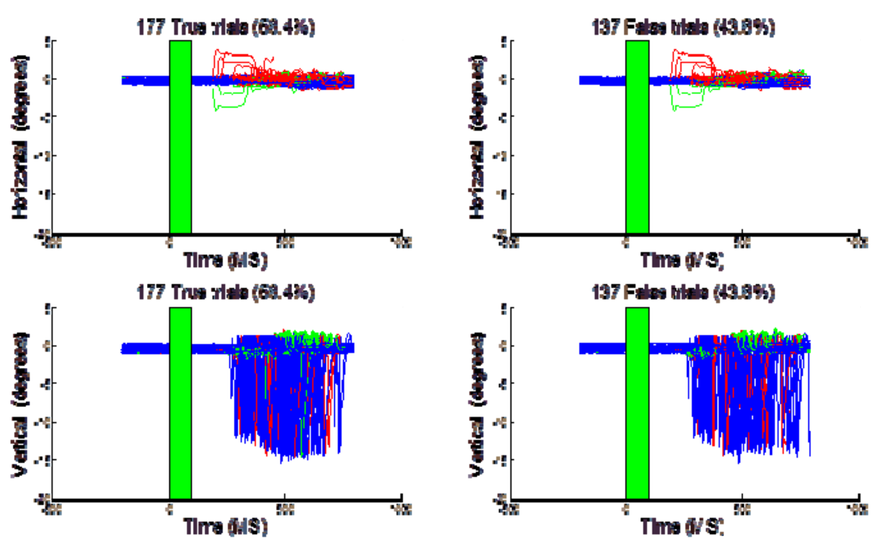

Figure 1 Eye tracking results for subject SF. The green bar shows the target duration.

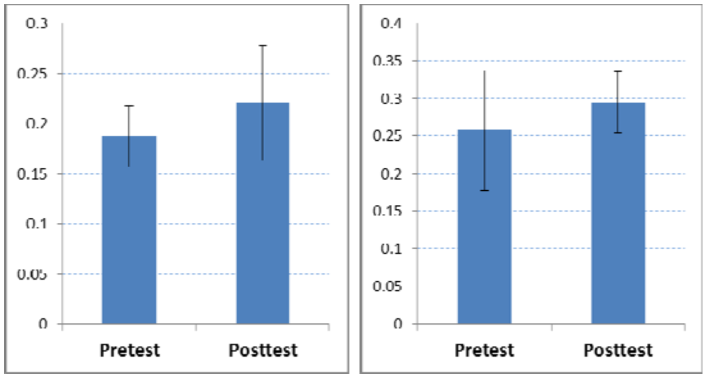

Figure 2 Training results of the healthy participants on gaze stability. Error bars, SEM.

Visual acuity measured with the ETDRS Chart:

Figure 3 shows the visual acuity measured using the ETDRS chart (left panel) before and after training (N=20). The zero line of the ETDRS chart indicates perfect vision (i.e., 20/20) and negative values indicate supervision. There was a significant improvement of visual acuity after training, both in the left eye (Fig. 3, middle panel, 0.07 ETDRS lines, $P < 0.001$) and in the right eye (Fig. 3, right panel, 0.05 ETDRS lines, $P < 0.004$), that is by 18% and 13%, respectively. Note, that this improvement was achieved from a starting point of vision that is better the perfect vision (i.e., pretest measurements below zero in log units) towards supervision.

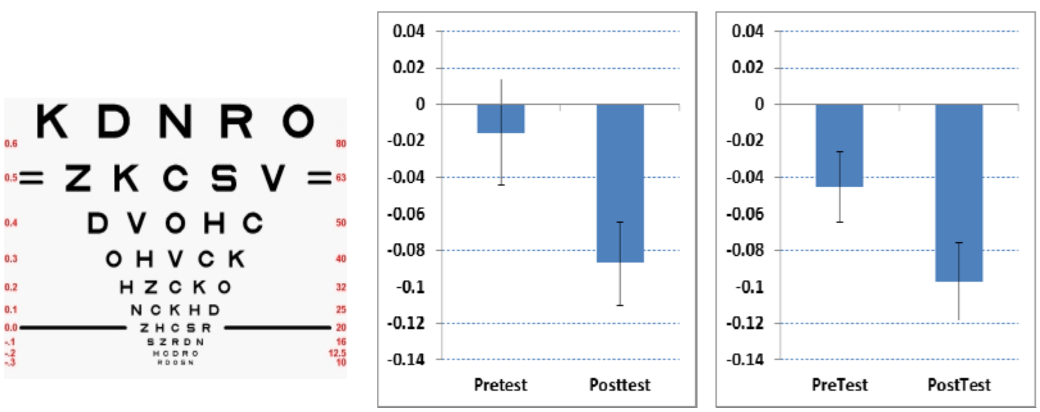

Figure 3 Training results of the healthy participants on ETDRS chart. Error bars, SEM.

Letter crowding (E-test):

Letter crowding during reading is the difficulty to identify letters in a line of text compared to easy identification in isolation. Crowding is widely acknowledged as a sensitive measure of visual acuity in the peripheral vision, similar to the ETDRS chart measurement of the visual activity in the fovea. Crowding increases with decreasing spacing between letters.

After training, crowding decreased with both the higher letter density (spacing of 4 letters) and the lower (spacing of 1 letter) (Fig. 4, N=19, one outlier, all differences are significant: $P < 0.05$). Note, that the magnitude of crowding reduction in peripheral vision is similar to the improvement on ETDRS chart in the fovea: 0.07 log units for the spacing of 1 letter and 0.05 for the spacing of 4 letters, equivalent to 18% and 13% improvement, respectively.

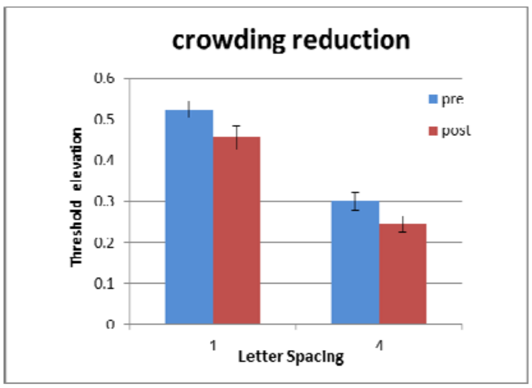

Figure 4 Training results of the healthy participants on E-test. Error bars, SEM.

Stereo Acuity:

After training, the stereo acuity was significantly improved for the two highest of the four tested disparities (Fig. 5, P= 0.18, 0.10, 0.01 and 0.03 for increasing disparities of 20, 40, 80 and 160 arcsec; N=19, one outlier). Note, that before training the threshod of 75% correct responses was above 180 arcsec and decreased dramatically after training to about 50 arcsec.

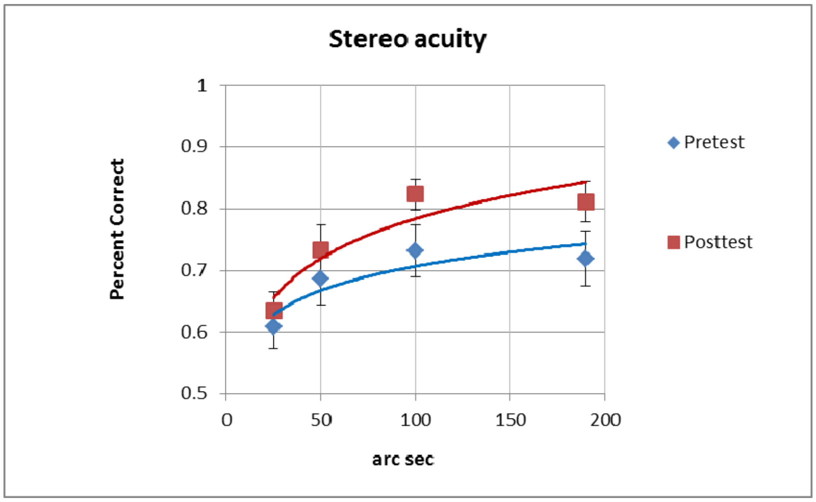

Figure 5 Training results of the healthy participants on stereo acuity for different spatial disparities. Error bars, SEM.

Transient Contrast Sensitivity:

After training, there was a significant improvement in contrast sensitivity measured with transient Gabor stimuli (Fig. 6, N=20 for fovea and N=19 (one outlier) for periphery). The improvement was evident both in the periphery (bottom left panel, all differences are significant in the periphery: P=<0.002)) and in the fovea (upper left panel, significant only for the lowest contrast of the target Gabor of 5%, an expected ceiling effect for high contrast that do not leave room for improvement: P<0.001). A similar pattern of results was observed for d-prime that is a sensitivity measure calculated from the probabilities of Hit and False-alarm responses (right panels).

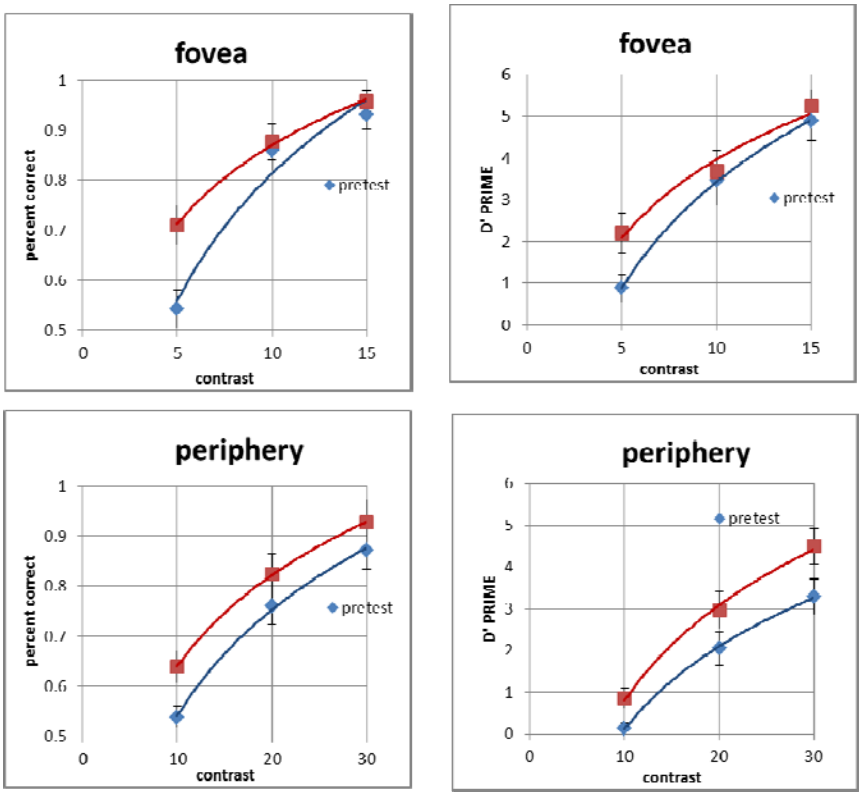

Figure 6 Training results of the healthy participants on a Transient Contrast Sensitivity task (Percent Correct and D-prime). Error bars, SEM.

Static Contrast Sensitivity under day vs. Night conditions:

There was a significant improvement in the static Contrast Sensitivity test (Fig. 7, N=20). Contrast sensitivity was measured "Day" and "Night" conditions, at 3 different spatial frequencies each (6, 9 and 12 cpd for "Day" and 3, 6, and 9 for "Night"). There are clear effects of the lightening conditions and of the spatial frequency on contrast detection, with significant improvement for the lowest spatial frequency of 6 cpd under "Day" conditions (upper panel, $P < 0.02$) and for the two lower spatial frequencies for the "Night" conditions (bottom panel, $P < 0.02$).

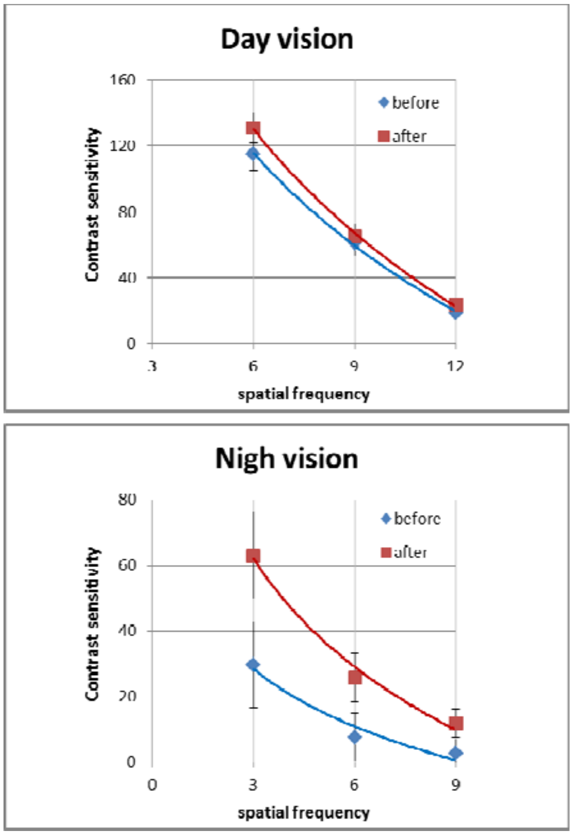

Figure 7 Training results of the healthy participants on a Static Contrast Sensitivity task under Day and Night conditions. Error bars, SEM.

1g. Post-treatment testing of the healthy participants (6-12)

See section 1f above.

1h. Data analysis and summary of the first year of the project (months 9-12).

In summary, the results of the training suggest that we will be able to apply a modified protocol to TBI patients. Upon analyzing the results of the control group, we have decided to improve the training technique and plan to run another subset of control group.

Task 2. To apply behavioral training to patients with traumatic brain injury-associated visual dysfunction (months 3-36):

2a. Recruitment of patients for the "No treatment control group" (months 3-18).

So far, all but one of the recruited patients will participate in the "Treatment group". We will recruit patients for the "No treatment control group" during the coming year once we have the treatment group. The ones that can't participate in the training but pass the inclusion criteria will participate in the no-treatment group.

2b. Recruitment of patients for the "Treatment group" (months 3-30).

Since the project has received the final approval for compliance with human subjects protection requirements only on Jul 30th 2011, a delay was posed on the stages of the study that involve human subjects. However, since we received the approval, we have started to recruit and test subjects very intensively. We have recruited 6 TBI patients so far. We present the results of a representative TBI patient in section 2d below. Other TBI patients are identified and are in the process of verification whether they pass the inclusion criteria.

2c. Baseline testing of all the patients (months 3-30).

See section 2d below.

2d. Training of the patients of the "Treatment group" (months 12-30).

Figure 8 shows visual acuity measurements using the ETDRS chart for the representative subject at pretest and now (Oct 2012). Visual acuity in the normal controls before training is zero (20/20). There is already a pronounced improvement in the visual acuity, of more than 1 ETDRS line (about 26% improvement), towards the levels of the normal control group. The training phase continues.

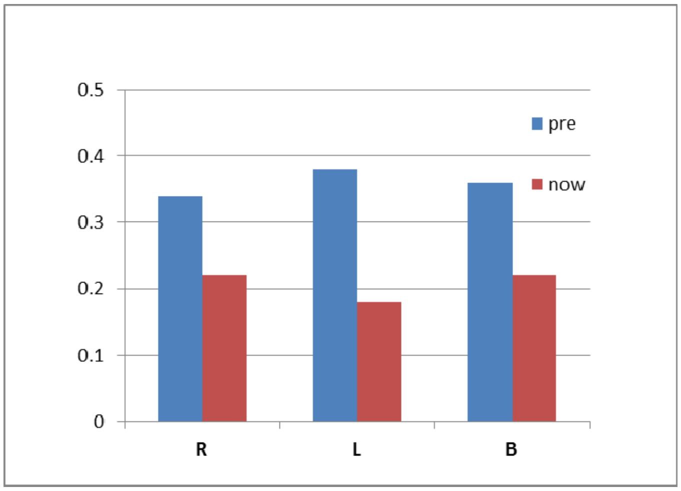

Figure 8 Improvement on ETDRS during on-going training (between April 2012 and October 2012) for a representative TBI subject.

Figure 9 shows contrast sensitivity measurements for static targets for the representative subject at pretest and now (Oct 2012), compared to measurements in the normal controls before training for the same spatial frequencies (as shown in Fig. 7). There is already a pronounced improvement for both spatial frequencies (9 and 12 cpd), towards the levels of the normal control group.

Moreover, since the training methodology is based on lateral interactions between neurons, we tested the effects that flanking Gabors induced on the target GAbors for the spatial separation that induces a positive effect in normal controls ("facilitation", as published in Polat and Sagi, 1993). The positive effect of lateral interactions reduces the detection threshold of the target Gabor, whereas a negative effect, also termed "lateral masking", induces threshold elevation for the target detection. As shown in Figure 10, for the spatial separation of 3 wavelengths, in contrast with a profound threshold reduction in normal controls, there was an opposite effect - threshold elevation – in the representative TBI patient before training. However, there is already a pronounced improvement in lateral interactions, with the negative effect of lateral masking replaced by a slight positive effect of facilitation (i.e., detection threshold reduction), towards the pattern that is found in normal controls.

This patient continues his training protocol and will be retested again.

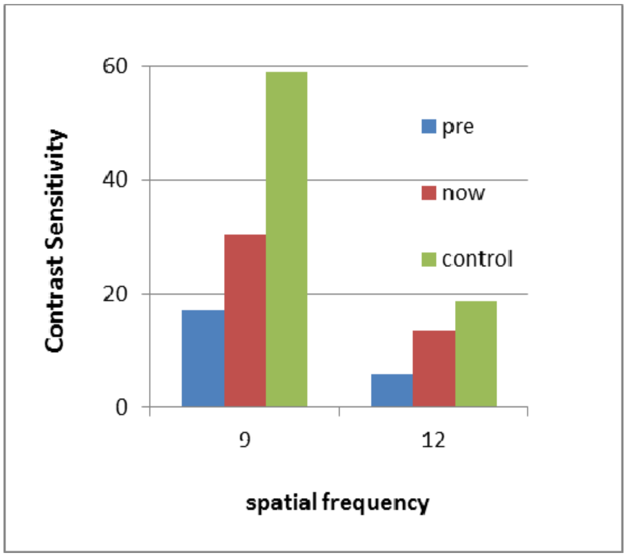

Figure 9 Improvement in contrast sensitivity during on-going training (between April 2012 and October 2012) for a representative TBI subject.

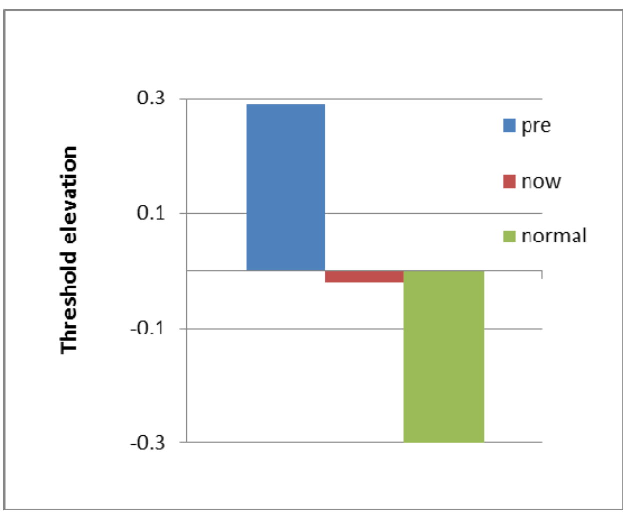

Figure 10. Improvement in lateral interactions measured as lateral masking, during on-going training (between April 2012 and October 2012) for a representative TBI subject.

Key Research Accomplishments

- Accomplishment in the control group experiments.
- Achievement of a real outcome of improvement of visual functions that has an impact on the everyday functions.
- Validation of the training protocol suitability for patients.
- Recruitment of patients.
- Solving technological problems to enable training of patients at their homes
- Training of patients.
- Intensive screening the medical files to identify more potential TBI patients.

Reportable Outcomes

- Data presentation in the 3rd International Workshop on Perceptual Learning in December 2012.
- Preparation of a manuscript for publication based on the data of all controls subjects.
- Recruitment of 2 research assistants
- Recruitment of a dedicated technician to set-up and follow-up training of patients at their homes

Conclusion

Despite administrative difficulties that delayed the initiation of the protocol parts involving human subjects, to date, we have completed the initial pretests, the training and the posttests in the control group. There was a remarkable improvement in the objective measurements of the visual functions, including subjective improvement reported by the subjects. After analyzing the posttest results, we plan to refine and test a slightly different training protocol in order to achieve the optimal protocol for training the TBI patients. Six TBI patients were recruited to participate in the study. The particiapnts that are training feel subjective improvement in the everyday life. More participants were approached and are entering the study in the coming quarter, depending on their rehabilitation schedule and the limitation determined by the minimal elapsed period of one year after the TBI as required by the study protocol.

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